

ABSTRACT

Diabetes is characterized by development of specific microvascular complications and by a high incidence of accelerated atherosclerosis.

The assumption underlying current clinical treatment is that lowering the level of time-averaged glucose concentration, measured as hemoglobin A1c (HbA1c), prevents the development and progression of microvascular complications. This current treatment recommendation, adopted by diabetes professional societies around the world, is based on data from the 1993 Diabetes Control and Complications Trial (DCCT). Recent Diabetes Control and Complications Trial data analyses show that 89% of the variation in microvascular complications risk in type 1 diabetes is not captured by HbA1c values (time-averaged glucose concentration). Recent experimental evidence from Dr Brownlee's lab, shows that transient exposure to threshold levels of high glucose reprograms human endothelial cells to continue overproducing reactive oxygen species in the presence of physiologic glucose concentrations. This persistent ROS overproduction causes an equally persistent overexpression of pro-inflammatory genes in normal glucose due to histone modifications in the proximal promoter of the NF- κ B subunit p65. Since in normal cells the epigenetic changes are rapidly reversed by histone demethylases and histone methyltransferases my thesis work aimed to understand how transient exposure to high glucose reprograms endothelial cells, and characterize the critical regulatory networks that shift vascular endothelial cells to a state of persistent excess ROS production after transient exposure to high glucose.

We found that transient spikes of hyperglycemia cause persistent mitochondrial overproduction of ROS during subsequent periods of prolonged normal glucose, causing persistent activation of the epigenetic changes and resultant vascular inflammatory gene expression. We identified a multi-component positive feedback loop induced by transient exposure to high glucose in human vascular endothelial cells which maintains persistently increased ROS production in normal glucose, thus we verified that transient disruption of any of the elements in the feed back loop rapidly restores the system to its normal state, including reversing persistent increased ROS production, persistent hyperglycemia-induced epigenetic changes and persistent increased NF- κ B-dependent pro-inflammatory gene expression.

Our results highlight the dramatic and long-lasting effects that short-term hyperglycemic spikes can have on vascular cells and suggest that transient spikes of hyperglycemia may be an HbA1c-independent risk factor for diabetic complications. Moreover we understood the mechanism underlying the continue overproducing of reactive oxygen species in the presence of physiologic glucose concentrations in human endothelial cells. This knowledge will provide the basis for developing new type 1 diabetes treatment paradigms that more effectively prevent the development and progression of microvascular complications.